



INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification ⁵ : A61K 37/02, C07K 5/08, 5/06	A1	(11) International Publication Number: WO 92/21368 (43) International Publication Date: 10 December 1992 (10.12.92)
(21) International Application Number: PCT/US92/04653 (22) International Filing Date: 4 June 1992 (04.06.92) (30) Priority data: 711,530 6 June 1991 (06.06.91) US (60) Parent Application or Grant (63) Related by Continuation US 711,530 (CON) Filed on 6 June 1991 (06.06.91) (71) Applicant (for all designated States except US): LIFE SCIENCES' TECHNOLOGIES, INC. [US/US]; 2001 Park Place, Suite 495, Birmingham, AL 35203 (US).	(72) Inventor; and (75) Inventor/Applicant (for US only) : MAHNAZ KHALED, F. [US/US]; 6553 Quail Run Drive, Pelham, AL 35124 (US). (74) Agents: WARBURG, Richard, J. et al.; Lyon & Lyon, 611 West Sixth Street, 34th Floor, Los Angeles, CA 90017 (US). (81) Designated States: AT (European patent), AU, BB, BE (European patent), BG, BR, CA, CH (European patent), DE (European patent), DK (European patent), ES (European patent), FI, FR (European patent), GB (European patent), GR (European patent), HU, IT (European patent), JP, KP, KR, LK, LU (European patent), MC (European patent), MG, MW, NL (European patent), NO, PL, RO, RU, SD, SE (European patent), US. Published <i>With international search report.</i>	
(54) Title: COMPOSITION AND METHOD FOR DISEASE TREATMENT		
(57) Abstract A composition and method for its use in treatment of an immune disorder in a mammal. The composition includes, in relative amounts, between 50 and 3000 mg of a purified compound selected from oxidized and unoxidized gamma-L-glutamyl-L-cysteinylglycine, gamma-L-glutamyl-L-cysteine, N-acetyl-L-cysteine, N-acetyl-L-cysteine-glycine, and any other pharmaceutically active compound which directly enhances the level of gamma-L-glutamyl-L-cysteinylglycine in a mammal, and any salt or ester of said compound, between 50 and 3000 mg purified L-glutamine, between 50 and 10,000 mg purified vitamin C, between 50 and 500 mg purified vitamin E, between 10 and 100 mg purified Beta-carotene, and between 1 and 25 mg purified vitamin B ₆ .		

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DESCRIPTIONComposition and Method for Disease TreatmentBackground of the Invention

This invention relates to nutritional supplements.

The human diet is the subject of many standard texts. Such a diet may include use of dietary supplements, e.g.,
5 in the form of pills or liquids, which may include one or more vitamins, minerals, and essential or non-essential amino acids. In addition, it is common for people to alter their diet to change their input of fats or lipids, proteins, and carbohydrates.

10 It is recognized that the diet of a person may have some affect on their health. For example, Corman, 69 Med. Clin. North Am., 759, 1985 describes the influence of specific nutrients on specific immune mechanisms; Huang et al., 34 Clin. Chem. 1957, 1987 describe malnutrition in
15 persons infected with the virus HIV, manifested by deficiency in several essential nutrients; Herzlich et al., 33 Am. J. Hematol 177, 1990 describe the effect of treatment of Acquired Immunodeficiency Syndrome (AIDS, caused by HIV infection) with 3'-azido-3' deoxythymidine (AZT),
20 including the depletion of folic acid and vitamin B₁₂, and is unclear "whether the benefit [of folate or vitamin B₁₂ supplementation] exceeds the risks...;" Moseson et al., 2 J. Acquired Immune Deficiency Symptoms, 235, 1989 state that "recommendations for dietary supplementation in HIV-
25 infected individuals are premature and possibly hazardous;" and Roederer et al., 87 Proc. Natl. Acad. Sci. USA, 4884, 1990, suggest N-acetyl-L-cysteine as "a possible therapeutic agent in AIDS."

Glutathione and related compounds are suggested as
30 therapeutic agents by Tognella et al., U.S. Patent 4,871,528, (to treat tumors); Pilotto et al., U.S. Patent 4,761,399 (to treat pathologic syndromes); Kitahara et al., U.S. Patent 4,927,808 (to treat necrosis and a

multitude of related diseases); Asano et al., U.S. Patent 4,968,671 (to treat ischemic heart disease); and Naylor, U.S. Patent 4,466,978 (to lower bodyweight). Reduced glutathione is a free radical scavenger in cells which is usually recycled in vivo from oxidized glutathione with the help of nutrients such as vitamins C, and E, BETA-carotene, selenium, and chromium. Some dipeptides, including N-acetyl cysteine are capable of increasing glutathione levels in the plasma (Pilotto et al., supra and Kitahara et al., supra).

Summary of the Invention

Applicant has discovered that a nutrient composition can be used as an adjunct to therapeutic drugs in treatment of diseases affecting the immune system, as well as in other diseases or injured states. Without being bound to any theory, applicant believes that provision of the nutrients within this nutrient composition aids in increasing the amount of replication of the causative organism of the disease, and thus enhances the effect of drugs which exert maximum effectiveness on growing organisms. In addition, such nutrients increase the health of a patient to which they are administered. Thus, the nutrient composition and any standard drug treatment act synergistically to increase the quality of life, and life expectancy of a patient.

Applicant has recognized that the body's immune system can be compromised because of poor dietary habits or starvation, various environmental stresses that include physical, psychological, infection, trauma, ischemia, radiation, chemical exposure, cigarette, alcohol or narcotic substance abuse, and the toxic effect of one or more therapeutic drugs. A paradigm of such stress is found in AIDS, which appears to involve several nutritional aberrations. HIV is a T-cell lymphotropic retrovirus that severely infects T-helper cells, and causes severe malnutrition. Such malnutrition increases the susceptibility

of the patient to opportunistic diseases that form the basis of AIDS or AIDS related complex (ARC). Among the deficient nutrients in AIDS patients, or in HIV-infected patients, are anti-oxidants such as vitamins A, C, and E, and glutathione (gamma-L-glutamyl-L-cysteinylglycine).

Applicant proposes that the above-described immune disorders which are caused by a virus and/or bacterium can be treated by using antiviral and/or antibacterial pharmacological agents (generically called antiorganism agents), together with a nutritional supplement which both bolsters the immune competence of the patient, and reduces the toxicity of the antiorganism agent. The nutritional supplement accelerates replication of the causative virus or bacterium, and creates an ideal condition for the anti-organism agent to exert its maximum effectiveness in killing or injuring the organism. A specific composition of this mixture of nutrients is provided in Table 1 where the appropriate relative ranges of each nutrient in the mixture is noted. These ranges reflect the variation in individual patient requirements. Such requirements will depend on body weight, age, sex, and the type of disease to be treated. In general, this range is ideal for provision within a capsule, pill, or liquid tonic for oral administration to a 70 kg human.

TABLE 1: Individual Nutrient and the Ranges in Necessary Quantity of each Nutrient

<u>Nutrients</u>		<u>Ranges of Amount</u>	
5	L-Arginine	50	- 5,000 mg
	Beta-Carotene	10	- 100 mg
	Chromium	5.0	- 50 μ g
	Folic Acid	50	- 150 μ g
	L-Glutamine	50	- 3,000 mg
10	Glutathione	50	- 3,000 mg
	Iron	1.0	- 50 mg
	Magnesium	10	- 50 mg
	Pantothenic Acid	5	- 50 mg
	Riboflavin	1.0	- 25 mg
15	Selenium	10	- 1,000 μ g
	Thiamine	5	- 50 mg
	Vitamin A	0.5	- 10 mg
	Vitamin B ₆	1.0	- 25 mg
	Vitamin B ₁₂	0.5	- 50 μ g
20	Vitamin C	50	- 10,000 mg
	Vitamin E	50	- 500 mg
	Zinc	1.0	- 50 mg

The nutrients described in Table 1 can be used in the form of physiologically acceptable salts and esters thereof. The glutathione may be in its oxidized or reduced form or may be replaced with any of its immediate biochemical precursors, such as gamma-L-glutamyl-L-cysteine, N-acetyl-L-cysteine, and N-acetyl-L-cysteine-glycine, and their salts or esters, or any other pharmaceutically active compound that directly enhances the level of glutathione in the patient. Examples of such compounds are well known to those in the art, and are found, *inter alia*, in Pilotto et al., *supra*. By "directly enhances" is meant that the compound is converted into glutathione by only one or two biochemical reaction steps; the phrase does not include compounds, such as glucose, which eventually may be converted to glutathione.

Thus, in a first aspect the invention features a composition adapted for treatment of an immune disorder in

a mammal. This composition comprises, consists, or consists essentially of the amounts shown in Table 1 of a purified compound selected from oxidized and unoxidized gamma-L-glutamyl-L-cysteinylglycine, gamma-L-glutamyl-L-cysteine, N-acetyl-L-cysteine, N-acetyl-L-cysteinylglycine, and any other pharmaceutically active compound which directly enhances the level of gamma-L-glutamyl-L-cysteinylglycine in a mammal, and any salt or ester of said compound, purified L-glutamine, purified vitamin C, purified vitamin E, purified Beta-carotene and purified vitamin B₆. Generally, such a composition is provided within any pharmaceutically-acceptable buffer.

In preferred embodiments the composition is provided with one or more (preferably all) of the following purified components in an amount shown in Table 1: L-arginine, chromium, folic acid, iron, magnesium, selenium, pantothenic acid, riboflavin, thiamine, vitamin A, vitamin B₁₂, and zinc.

By "purified" is meant that the compound or specific component is provided in a form acceptable by the United States Food and Drug Administration for administration to an animal or human patient. The term is meant to exclude provision of the specific component as part of an animal or plant which may be eaten by the mammal to be treated. In general such compounds and components will be provided in a very pure form commonly used in formulating existing vitamin pills and the like.

In a related aspect, the invention features a method for a treatment of immune disorders such as Acquired Immunodeficiency Syndrome, Herpes Infection, Hepatitis, or the disorder caused by traumatic injury, cancer, or diabetes, by administration of a composition as described above. The composition is provided in an amount sufficient to alleviate one or more symptoms of the immune disorder.

By "symptom" is meant the outward signs, as well as any measurable indicia, of a disease state commonly recog-

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nized as indicative of the disease to be treated by medical doctors or veterinarians of ordinary skill in the art.

In a related aspect, the invention features a method for treatment of an immune disorder in a mammal. A mammal
5 having such a disorder caused by a virus or bacterium is identified, and the mammal then provided with an antiviral or antibacterial agent with some toxicity to the mammal (i.e., having some affect on the nutritional state of the mammal), and a nutritional composition (as described
10 above) in an amount sufficient to reduce the toxicity of the agent and accelerate replication of the virus or bacterium.

In addition, the invention includes a similar method for treatment of cardiovascular disease, mental disease,
15 drug addition, and hair loss in a mammal, with the composition being provided in an amount sufficient to alleviate one or more symptoms of such diseases or conditions.

Examples of cancers which may be treated include Karposi's Sarcoma, lymphoma, and non-Hodgkin lymphoma; the
20 disease is preferably treated simultaneously with some drug therapy, such as AZT, in an amount sufficient to alleviate a symptom of the disease; the causative organism of the infection is HIV, herpes virus, hepatitis virus, or a virus or bacterium causative of a respiratory disorder;
25 the injury is a traumatic injury resulting from fractures, laceration or burns; the disease may be high blood pressure, hypertension, obesity or ischemic heart disease; in addition, the disease may be tardive dyskinesia, and hyperactivity in children; and the addiction may be
30 addiction to psychoactive drugs, narcotic drugs, nicotine or alcohol.

The above nutritional composition, and methods for use of that composition, have been found to significantly enhance the efficacy of treatment of diseases in conjunction
35 with one or more routine drug therapies. The effect is profound and unexpected, in that many symptoms of severe diseases can be significantly alleviated.

Other features and advantages of the invention will be apparent from the following description of the preferred embodiments thereof, and from the claims.

Description of the Preferred Embodiments

5 The drawing will first briefly be described.

Drawing

The drawing is a graphical representation of results of experiments comparing the use of AZT alone, and AZT with a nutrient composition of the invention.

10 Nutrient Composition

The nutrient composition is generally described above. Those of ordinary skill in the art will recognize that the most important components of this nutrient composition include glutathione, or its equivalent, in combination with glutamine, vitamins E and C, and Beta-carotene. However, it is preferred that all of the components listed in Table 1 be included for full treatment of the various diseases discussed below.

20 An example of the use of the nutrient composition described in Table 1 for treatment of cells infected with HIV, or humans infected with HIV is provided below. Those of ordinary skill in the art will recognize that this example is not limiting in the invention, and that such a nutrient composition can be readily used in treatment of the other diseases discussed above. The nutrient composition is formulated by use of standard procedures and may be administered by any of a number of standard procedures, including oral administration, intramuscular, or intravenous injection.

30 Table 2 shows the precise chemical composition of the nutrient composition used in the examples below.

TABLE 2:

<u>Nutrients</u>		<u>Amount per capsule</u>
	L-Arginine	75 mg
	Beta-Carotene	15 mg
5	Chromium	15 μ g
	Folic Acid	100 μ g
	L-Glutamine	150 mg
	Glutathione	250 mg
	Iron	10 mg
10	Magnesium	20 mg
	Pantothenic Acid	25 mg
	Riboflavin	10 mg
	Selenium	25 μ g
	Thiamine	10 mg
15	Vitamin A	4 mg
	Vitamin B ₆	8 mg
	Vitamin B ₁₂	1.0 μ g
	Vitamin C	500 mg
	Vitamin E	150 mg
20	Zinc	25 mg

Example 1: In Vitro Analysis

Following the procedures of Wieslow et al. 81 Journal of National Cancer Institute 577, 1989, (hereby incorporated by reference herein) T₄ lymphocytes (CEM cell line) 25 were used in a soluble-formazan assay to assess the toxicity of the test material (AZT \pm nutritional supplement) and the recovery of T-cells from HIV infection.

In-Vitro Assay

Briefly, the test sample was dissolved in dimethyl 30 sulfoxide and diluted 1:100 in RPMI cell culture medium to prepare serial half-log₁₀ dilutions. T₄ lymphocytes (CEM cell line) were added, and after about an hour HIV-1 added, resulting in a 1:200 final dilution of the test sample. Uninfected cells with the sample served as a control 35 for the toxicity of the test sample. Infected and uninfected cells without the test sample served as the basic control. The cultures were then incubated at 37°C in a 5% carbon dioxide atmosphere for six days. The tetrazolium salt was added to the wells and incubated 40 until the formazon color was developed by the viable

cells. Each well was analyzed spectrophotometrically to quantitate the formazan production, and also examined microscopically to detect viable cells. Test sample-treated virus-infected cells were compared to the test sample-treated noninfected cells, and with other appropriate controls on the same plate. The results are plotted graphically as described below.

Referring to the figure, the results are shown in graphical form for combination of AZT with the nutritional supplement described in Table 2, and for AZT alone.

Figure 1 displays a plot of the \log_{10} of the concentrations of the test sample as $\mu\text{g/ml}$ against the measured test values expressed as a percentage of the uninfected, untreated control values. The solid line connecting the rectangular symbols depicts the percentage of surviving HIV-infected cells treated with AZT, with or without the composition of Table 2, relative to uninfected, untreated controls and indicates the in vitro anti-HIV activity of the test samples. The broken line connecting the triangular symbols depicts the percentage of surviving uninfected cells treated with the test samples relative to the same uninfected, untreated controls, and expresses the in vitro growth inhibitory properties of the test samples. The viral cytopathic effect is given as the dotted reference line which indicates the extent of destruction of cells by the virus in the absence of treatment. The percent of protection calculated from the test results is presented on the right side of the graph. The therapeutic index (TI) of the test sample was estimated from the ratio of the values for 50% inhibitory concentration (IC_{50}) to the 50% values for the effective concentration (EC_{50}), i.e., $\text{TI} = \text{IC}_{50} / \text{EC}_{50}$.

The broken lines with triangular data points indicate the percent of uninfected T-cells. With AZT alone, about a 75% survival of T-cells was observed compared to control cells. With AZT and the nutritional supplement such survival was increased to approximately 150%. Thus, the sup-

plement enhances survival of T-cells in the presence of HIV.

5 The solid lines with rectangular data points indicate the therapeutic effectiveness of the material for the T-cells. With AZT alone, inhibition of growth of normal T-cells is observed, thus indicating toxicity. With a combination of AZT and the nutritional supplement, the growth is almost doubled. Thus, the nutritional supplement protects the cells from toxicity of AZT.

10 These data indicate that the therapeutic index of the drug nutrient combination therapy is almost ten times higher than that of AZT alone.

Example 2:

15 The above drug nutrient combination therapy was tested on three human subjects infected with HIV. Their clinical features are noted in Table 3.

TABLE 3:

Clinical Features of Patients
Receiving Immuno-Vite™

	<u>Patient No.</u> <u>& Diagnosis</u>	<u>Symptoms &</u> <u>Findings at</u> <u>Entry</u>	<u>Weeks on</u> <u>Nutri-</u> <u>tional</u> <u>Supplement</u>	<u>Clinical</u> <u>Observations</u>
5				
10	1. AIDS- Post- PCP	Weight loss, Papulovesicular rash fever, malaise, T ₄ =1%, T ₈ =47%	4	Weight gained, no fever, and rash dimin- ished. Total lymphocyte count went up, although T ₄ did not change, T ₈ went up.
15				
20	2. ARC	Weight loss, malaise, Lymphadenop- athy, yeast infection in gluteal area, rectal wart, T ₄ =320, T ₈ =1710	3	Weight gained, increased energy, no raised lymph nodes, no yeast infec- tions, dimin- ished rectal wart, T ₄ =450, T ₈ =1220.
25				
30	3. ARC	Edemic, rash, fever, oral candidiasis, mouth sores (difficulty in talking), dementia	2	Improved skin lesions, mouth sores improved (speak without difficulty), reduced confusion.
35				
	AIDS (Acquired Immune Deficiency Syndrome)			
	PCP (Pneumocystis Carinii Pneumonia)			
	ARC (AIDS-Related Complex)			

The patients were routinely taking AZT and other antiviral and antibacterial drugs. Clinical improvement of their condition was observed after only a short drug-nutrient combination therapy. Such significant improvements were observed within two weeks of initiation of the drug nutrient therapy.

Other embodiments are within the following claims.

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CLAIMS

1. A composition adapted for treatment of an immune disorder in a mammal, comprising:
between 50 and 3000 mg of a purified compound
5 selected from oxidized and unoxidized gamma-L-glutamyl-L-cysteinylglycine, gamma-L-glutamyl-L-cysteine, N-acetyl-L-cysteine, N-acetyl-L-cysteine-glycine, and any other pharmaceutically active compound which directly enhances the level of gamma-L-glutamyl-L-cysteinylglycine in a mammal,
10 and any salt or ester of said compound,
between 50 and 3000 mg purified L-glutamine,
between 50 and 10,000 mg purified vitamin C,
between 50 and 500 mg purified vitamin E,
between 10 and 100 mg purified Beta-carotene,
15 and
between 1.0 and 25 mg purified vitamin B₆.
2. The composition of claim 1, further comprising one or more of the following purified components:
between 50 and 5000 mg L-arginine,
20 between 5 and 50 μ g chromium,
between 50 and 150 μ g folic acid,
between 1 and 5 mg iron,
between 10 and 50 mg magnesium,
between 5 and 50 mg pantothenic acid,
25 between 1 and 2.5 mg riboflavin,
between 5 and 50 mg thiamine,
between 0.5 and 10 mg vitamin A,
between 10 and 1000 μ g selenium,
between 0.5 and 5 μ g vitamin B₁₂, and
30 between 1 and 50 mg zinc in an amount.
3. The composition of claim 2, wherein said composition comprises each said component.

4. The composition of claim 1 or 3 wherein said compound is N-acetyl-L-cysteine-glycine or an ester or salt thereof.

5. The composition of claim 1 or 3 wherein said compound is gamma-L-glutamyl-L-cysteinylglycine or an ester or salt thereof.

6. The composition of claim 1 or 3 wherein said compound is gamma-L-glutamyl-L-cysteine or an ester or salt thereof.

7. The composition of claim 1 or 3 wherein said compound is N-acetyl-L-cysteine or an ester or salt thereof.

8. A method for treatment of an immune disorder in a mammal, comprising the steps of:

identifying a mammal having an immune disorder caused by an organism chosen from a virus and a bacterium; providing to said mammal an antiorganism agent chosen from an antiviral and an antibacterial agent, said antiorganism agent having some toxicity to said mammal;

providing a composition comprising between 50 and 3000 mg purified compound selected from oxidized and unoxidized gamma-L-glutamyl-L-cysteinylglycine, gamma-L-glutamyl-L-cysteine, N-acetyl-L-cysteine, N-acetyl-L-cysteine-glycine, and any other pharmaceutically active compound which directly enhances the level of gamma-L-glutamyl-L-cysteinylglycine in a mammal, and any salt or ester of said compound,

between 50 and 3000 mg purified L-glutamine,
between 50 and 10,000 mg purified vitamin C,
between 50 and 500 mg purified vitamin E,
between 10 and 100 mg purified Beta-carotene,
between 1 and 25 mg purified vitamin B₆, and

introducing said composition into said mammal in an amount sufficient to reduce the toxicity of said anti-organism agent, and sufficient to accelerate the replication of the causative organism.

- 5 9. A method for treatment of an immune disorder in a mammal, comprising the steps of:
 identifying a mammal having an immune disorder;
 providing to said mammal a composition comprising:
- 10 between 50 and 3000 mg purified compound selected from oxidized and unoxidized gamma-L-glutamyl-L-cysteinylglycine, gamma-L-glutamyl-L-cysteine, N-acetyl-L-cysteine, N-acetyl-L-cysteine-glycine, and any other pharmaceutically
- 15 active compound which directly enhances the level of gamma-L-glutamyl-L-cysteinylglycine in a mammal, and any salt or ester of said compound,
- 20 between 50 and 3000 mg purified L-glutamine, between 50 and 10,000 mg purified vitamin C, between 50 and 500 mg purified vitamin E, between 10 and 100 mg purified Beta-carotene; between 1 and 25 mg purified vitamin B₆, and
- 25 introducing said composition into said mammal in an amount sufficient to alleviate one or more of the symptoms of said immune disorder.

10. The method of claim 8 or 9, wherein said immune disorder is an acquired immunodeficiency syndrome.

- 30 11. The method of claim 8 or 9, wherein said composition further comprises in one or more of the following purified components:
- between 50 and 5000 mg L-arginine,
 between 5 and 50 μ g chromium,
 between 50 and 150 μ g folic acid,

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between 1 and 5 mg iron,
between 10 and 50 mg magnesium,
between 5 and 50 mg pantothenic acid,
between 1 and 2.5 mg riboflavin,
5 between 5 and 50 mg thiamine,
between 0.5 and 10 mg vitamin A,
between 10 and 1000 μ g selenium,
between 0.5 and 5 μ g vitamin B₁₂, and
between 1 and 50 mg zinc.

10 12. The method of claim 11, wherein said composition comprises each said component.

13. The method of claim 8, or 9 wherein said compound is N-acetyl-L-cysteine-glycine or an ester or salt thereof.

15 14. The method of claim 8, or 9, wherein said compound is gamma-L-glutamyl-L-cysteinylglycine or an ester or salt thereof.

15 15. The method of claim 8, or 9, wherein said compound is gamma-L-glutamyl-L-cysteine or an ester or salt
20 thereof.

16. The method of claim 8, or 9, wherein said compound is N-acetyl-L-cysteine or an ester or salt thereof.

17. The method of claim 11 wherein said compound is N-acetyl-L-cysteine-glycine or an ester or salt thereof.

25 18. The method of claim 11 wherein said compound is gamma-L-glutamyl-L-cysteinylglycine or an ester or salt thereof.

19. The method of claim 11 wherein said compound is gamma-L-glutamyl-L-cysteine or an ester or salt thereof.

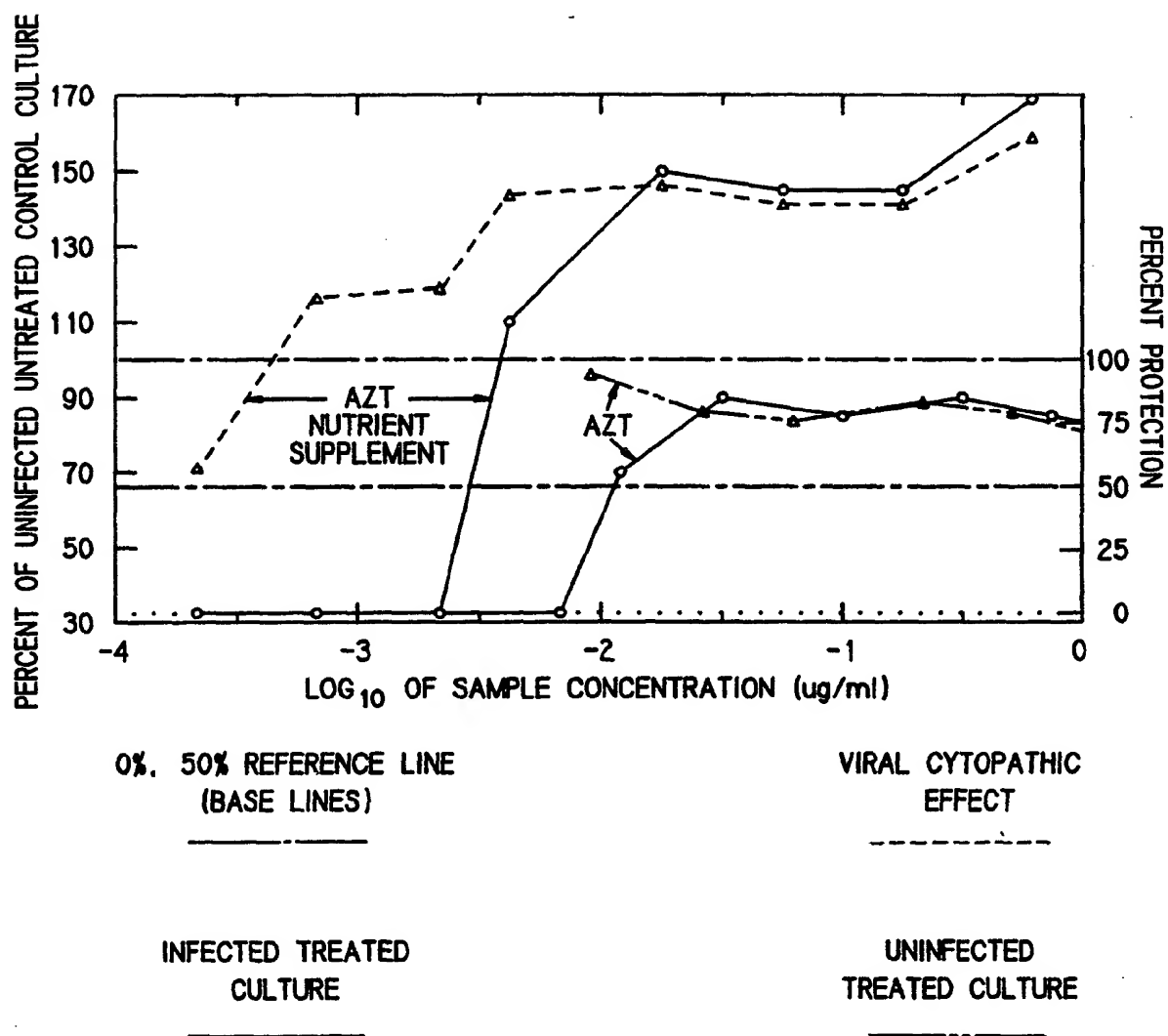
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20. The method of claim 11 wherein said compound is N-acetyl-L-cysteine or an ester or salt thereof.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US92/04653

A. CLASSIFICATION OF SUBJECT MATTER

IPC(5) : A61K 37/02 ; C07K 5/08, 5/06
US CL : 530/331; 514/19

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/331; 514/19

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS ONLINE, APS

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
<u>X</u> Y	US, A, 4,927,808 (Kitahara et al) 22 May 1990, see entire document.	<u>1-3,5-6</u> 4,7,8-20
<u>X</u> Y	US, A, 4,466,978 (Naylor) 21 August 1984, see entire document.	<u>1-3,5-6</u> 4,7,8-20
<u>X</u> Y	Proceeding of the National Academy of Science, vol.87, issued June 1990, Roederer et al, "Cytokine-stimulated Human Immunodeficiency Virus Replication Is Inhibited by N-acetyl-L-Cysteine", pages 4884-4888, see entire document.	<u>1-3,5-6</u> 4,7,8-20
Y	Journal of Acquired Immune Deficiency Syndromes, vol.2, No.3 issued 03 November 1989, Moseson et al, "The Potentential Role of Nutritional Factors in the Induction of Immunologic Abnormalities in HIV-Positive Homosexual Men", pages 235-247, see entire document.	4,7,8-20



Further documents are listed in the continuation of Box C.



See patent family annex.

* Special categories of cited documents:	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
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